

Glycopyrrolate: pharmacology and clinical use

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Summary

This is a review of glycopyrrolate whose function in clinical practice is compared with that of atropine.

Key words

Premedication; antisialogogue, glycopyrrolate.

Glycopyrrolate (pyrrolidinium 3-[(cyclopentyl-hydroxy/phenylacetyl)oxyl]-1,1-dimethyl bromide; glycopyrronium bromide; Robinul) the structure of which is shown in Fig. 1 is a quaternary ammonium anticholinergic drug. Originally synthesised in 1960,¹ it was extensively used in the 1960s for the treatment of peptic ulceration.²⁻⁵

The possible use of glycopyrrolate in anaesthetic practice was first described in 1970 by Boatright and his colleagues,⁶ who used it in premedication in an attempt to reduce the hazards of aspiration of gastric contents. Further early reports indicated that it could be used with advantage in place of atropine as an adjunct

to reversal by anticholinesterases of non-depolarising neuromuscular block.^{7,8} Although occasional reports continued to appear after that, it is only in the last 5 years that the drug has been studied extensively on both sides of the Atlantic. It is the object of this review to highlight the aspects of its actions which are most relevant to anaesthesia.

Pharmacology

In the animal studies of Franko and his colleagues,⁹ the most prominent pharmacological action reported was a profound and prolonged inhibition of gastro-intestinal tract motility and secretions. Pointers to the possible application of glycopyrrolate in anaesthetic practice in the original work of Franko *et al.*⁹ included profound and prolonged inhibition of salivation following parenteral administration and blocking of the peripheral but not the central effects of tremorine. In contrast to the marked central effects of atropine, glycopyrrolate had no effect on the electroencephalogram (EEG) in cats, suggesting that it did not penetrate the blood-

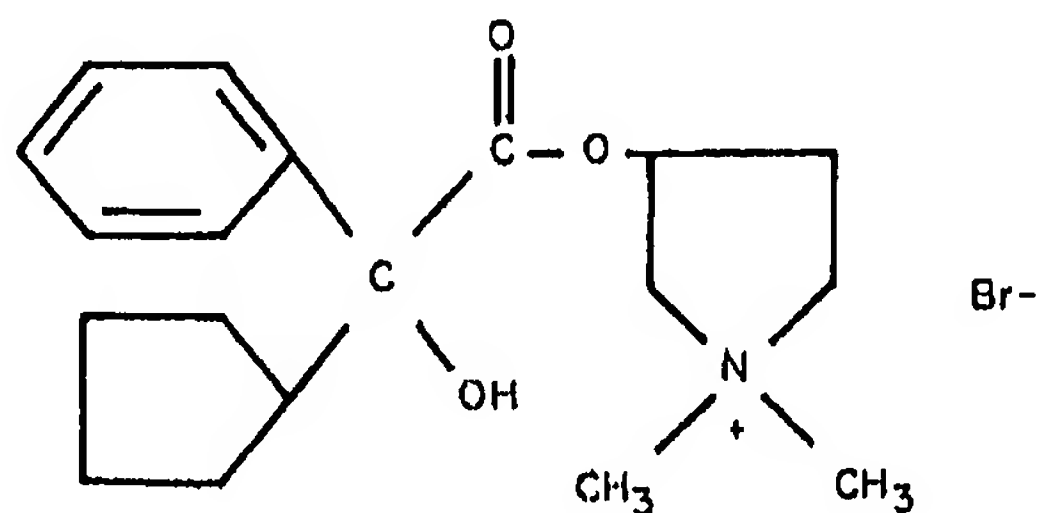


Fig. 1. Structure of glycopyrrolate.

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Table 1. Penetration of glycopyrrolate and atropine through the blood-brain and placental barriers; from Proakis and Harris¹⁰

	Maximum cerebrospinal fluid/serum ratio	Maximum fetal serum/maternal serum ratio
Glycopyrrolate	0.1	0.04
Atropine	0.87	1.00

brain barrier to any significant extent. This was confirmed by the study of Proakis and Harris¹⁰ who, using radiolabelled compounds, demonstrated clearly the ease with which atropine penetrated through the lipophilic blood-brain and placental barriers and the extremely poor passage of glycopyrrolate (Table 1).

Although the effects of glycopyrrolate on salivary secretion in volunteers were reported by Wyant and Kao in 1974,¹¹ it was not until 1978 that a comprehensive evaluation of the anti-muscarinic effects of the drug was reported in man.¹² In this study, healthy volunteers received three doses of glycopyrrolate (0.1, 0.2, and 0.4 mg) intramuscularly, three doses (0.1, 0.14, and 0.2 mg) intravenously and three doses (2.0, 4.0, and 8.0 mg) orally. Their effects on salivation, sweat gland activity, heart rate, pupil size and visual accommodation were recorded. The most prominent feature observed was a dose related inhibition of salivary secretion which persisted for over 6 hours after the largest parenteral doses. The antisialogogue effect was shown to be about five times as potent as that of atropine (Fig. 2).¹³ While Wyant and Kao¹¹ suggested that glycopyrrolate was twice as potent an antisialogogue as atropine in volunteers, their results were based on studies with only one dose of atropine and two of glycopyrrolate. The estimates of relative potency given by Mirakhur and Dundee¹³ were based on dose response curves employing three doses of each drug. As will be expected from a highly ionised quaternary ammonium compound the oral absorption was poor and erratic; for a 50% reduction in salivary secretion an oral dose 35 times greater than a parenteral dose was necessary. Sweat gland activity was similarly reduced following glycopyrrolate administration.¹²⁻¹⁴ Interestingly, the other parameters were unaffected indicating some degree of specificity (Fig. 3).

In the comparative study of Mirakhur and

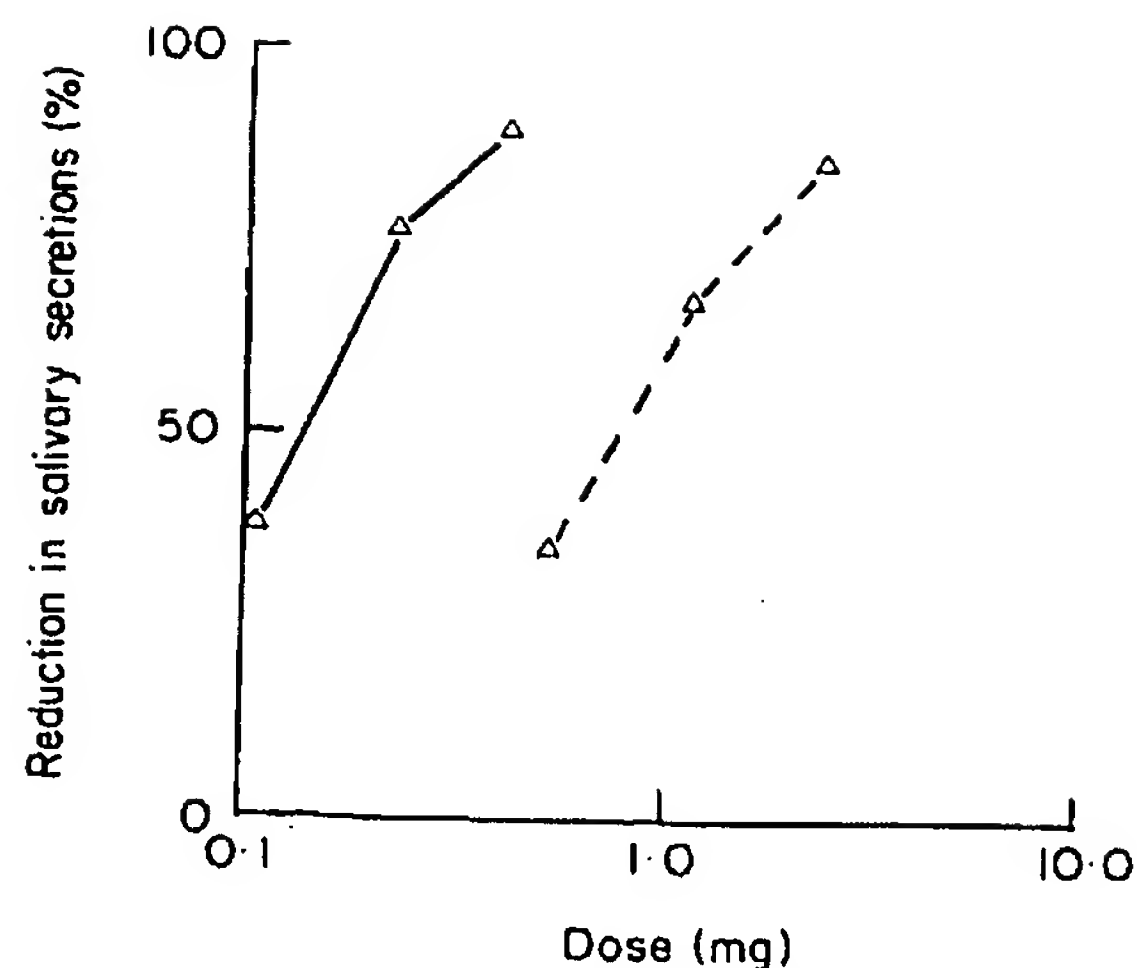


Fig. 2. Effects of glycopyrrolate (—) and atropine (---) on salivary secretion. (Reproduced by kind permission of the Journal of Royal Society of Medicine.¹³)

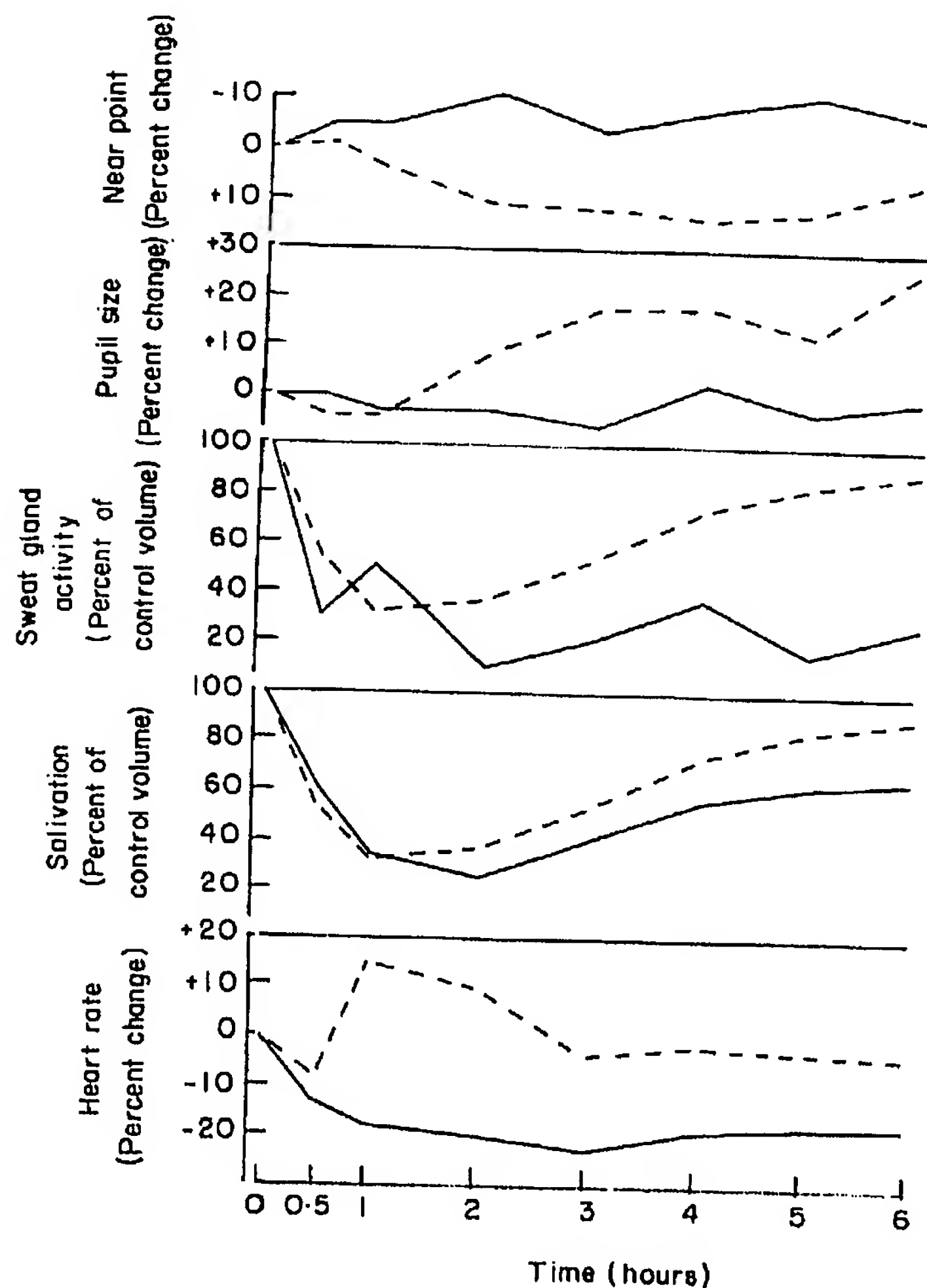


Fig. 3. Effects of atropine (---) and glycopyrrolate (----) on some aspects of cholinergic function. (Reproduced by kind permission of the Journal of Royal Society of Medicine.¹³)

Dundee referred to above, the essential difference in the clinical pharmacology of glycopyrrolate and atropine administered by the intramuscular routes to volunteers were also highlighted. Both drugs produced a dose related inhibition of salivation. However, in the doses studied, glycopyrrolate produced no increase in heart rate whereas atropine elicited a highly significant and dose-related tachycardia. Indeed, when the doses which were necessary to produce a 75% inhibition of salivation were compared, it was found that atropine produced a rise in heart rate of over 15% whereas this was not observed with glycopyrrolate.

Studies in conscious healthy volunteers have consistently shown an absence of significant effects on heart rate and rhythm following doses of glycopyrrolate which might be used in premedication.^{11,12,15,16} In anaesthetized patients, using larger intravenous doses, glycopyrrolate and atropine both produced a rise in heart rate with glycopyrrolate being approximately twice as potent (w/w) as atropine.¹⁷ The effects of the drug on heart rate in conscious adult patients are not well documented, particularly with reference to dose-response relationships. However, the effects on heart rate are quite apparent in anaesthetised patients.

The use of glycopyrrolate in children was first described by Wong and his colleagues¹⁸ who used it in the reversal of competitive neuromuscular block by neostigmine. However, its effects on heart rate and rhythm in conscious or anaesthetised children have only recently been studied. Although Lavis, Lunn and Rosen¹⁹ suggested that intravenous glycopyrrolate had a negligible effect in non-anaesthetised children one minute after its administration, other workers²⁰ found significant increases in heart rate over a 5-minute period in conscious children and children anaesthetised with halothane. The difference in these results can be explained by the fact that glycopyrrolate exerts its peak effect considerably later than one minute after its administration. The latter study also showed that glycopyrrolate was approximately twice as potent (w/w) as atropine in its effect on heart rate in children. Another study²¹ showed that both glycopyrrolate and atropine produced greater increases in heart rate during halothane than during enflurane anaesthesia in children. Accelerated junctional rhythm was the most common dysrhythmia observed in both these studies.

No significant effects on ventilation were found in the early animal studies.⁹ More recently it has been shown that glycopyrrolate has a significant and prolonged bronchodilating action, leading to an increase in dead space similar to that following the administration of atropine but persisting for a longer period of time.^{22,23}

Apart from the differences already mentioned, glycopyrrolate and atropine also differ in their effects on the eye. No significant increase in pupil size nor any recession in the near point of vision were observed in the earlier studies in volunteers,^{15,24} and this was confirmed in the more recent studies.^{12,25} Comparing glycopyrrolate and atropine, Mirakhur and Dundee¹³ showed significant and perceptible effects of atropine on the eye in the form of mydriasis and recession of the visual near point; these were not observed with glycopyrrolate. There are no changes in intraocular pressure in healthy volunteers²⁵ but neither were changes observed with atropine following normal premedicant doses.

There are only minimal changes in temperature in healthy adult volunteers.¹²

The studies in animals and healthy volunteers thus clearly show considerable differences in the pharmacological actions of glycopyrrolate and atropine. The most important of these are summarised in Table 2.

Table 2. Summary of the principal effects of atropine and glycopyrrolate in volunteers

	Atropine	Glycopyrrolate
Salivation	Marked inhibition	Marked and prolonged inhibition
Sweat glands	Marked inhibition	Marked and prolonged inhibition
Heart rate	Increase	Minimal change
Pupil size	Increase	No change
Near point of vision	Increase	No change

Absorption, distribution and metabolism

This has been studied with ¹⁴C-labelled glycopyrrolate in the mouse.²⁶ Following intravenous

administration, peak radioactivity was found in all organs at 5–10 minutes except brain; liver, kidney and intestines showed traces of activity at 24 hours. Following oral administration, stomach and small intestine showed the maximum amount of radioactivity and absorption from the gastrointestinal tract was poor.

Minimal amounts of glycopyrrolate cross the blood brain barrier.¹⁰ Both animal and human studies show that placental transfer is limited.^{10, 27, 28}

Studies of the metabolism of glycopyrrolate in animals²⁹ indicate the major metabolic pathway to be hydroxylation of the cyclopentyl ring and oxidation of the hydroxyl group in the mandelic acid residue. These metabolites have been mainly detected in the liver and kidney.²⁶

A study using intravenous ³H-glycopyrrolate in humans³⁰ showed the disappearance of more than 90% from the serum in 5 minutes and almost 100% in 30 minutes. Urinary radioactivity was highest in the first 3 hours and 85% was excreted in the urine within 48 hours. Paper chromatography showed 80% of the radioactivity in bile and urine corresponding to unchanged glycopyrrolate. Following oral administration to mice, 7.6% was excreted in the urine and about 79% in the faeces.²⁶

Glycopyrrolate in anaesthetic practice

The use of anticholinergic drugs in anaesthesia is in premedication, during anaesthesia and surgery and with anticholinesterase drugs at the end of anaesthesia for the antagonism of competitive neuromuscular block. Glycopyrrolate has been studied extensively in all these situations.

Premedication and peroperative use

The first report on the use of glycopyrrolate in anaesthetic practice involved its use in premedication in children for the prevention of the serious hazards of accidental aspiration of gastric contents during tonsillectomy.⁶ Here glycopyrrolate was used along with an alkali but a subsequent study³¹ confirmed the ability of the drug alone in children to raise the pH of gastric contents to safe levels with a concomitant reduction in the volume of gastric contents.

A further report by Baraka and his colleagues³² suggested that glycopyrrolate was

superior to atropine at raising the pH of gastric contents in parturients, although the accuracy of the statistical data from this study has been questioned.³³ Studies by other workers^{34–36} have failed to support the superiority of glycopyrrolate over atropine in this respect and this effect is likely to be achieved either with only high doses and consequent subjective discomfort, or when the drug is administered concurrently with alkalis by the oral route.³⁷ However, a proper comparison with atropine is difficult, due to the lack of data on equipotent dosages for this effect. It must also be remembered that glycopyrrolate, like atropine, reduces the opening pressure of the lower oesophageal sphincter^{38, 39} and like other anticholinergic drugs would reduce motility. Theoretically, these conditions could be associated with an increased incidence of regurgitation. In practice, however, a majority of anaesthetists use an anticholinergic drug in obstetric anaesthesia routinely,⁴⁰ with a rapid intravenous induction and application of cricoid pressure. In this situation the use of glycopyrrolate would be advantageous since it does not cross the placenta and has been shown to have no demonstrable effect on fetal heart rate.²⁸

The majority of anaesthetists use anticholinergic drugs in premedication for more conventional reasons, such as the drying of secretions and the inhibition of vagally-mediated falls in heart rate.⁴⁰ The earlier studies of its use in premedication^{41, 42} showed that it was an effective antisialogogue premedicant and other recent reports^{43–45} of its routine premedicant use confirmed these views. McCubbin and his colleagues,⁴⁵ who compared 0.2 mg glycopyrrolate and 0.6 mg atropine given intramuscularly about an hour pre-operatively, showed that while the two drugs had a similar antisialogogue effect, atropine was associated with tachycardia before induction in a large number of patients. In the study by Mirakhur and colleagues⁴⁴ where the drug was evaluated at three dose levels, 0.2 mg of glycopyrrolate was found to be a sufficient dose for premedication in average adults. However, they also observed that there was no need for routine anticholinergic premedication in patients undergoing mostly minor surgery. In other studies,^{43, 46} where single doses of suxamethonium were administered followed by laryngoscopy and tracheal intubation, it was found that premedication with glycopyrrolate was associated with a significantly lower incidence

of dysrhythmias during induction of anaesthesia than atropine following equipotent antisialagogue doses. Again, the omission of anticholinergic premedication was associated with a lack of dysrhythmias. With currently used anaesthetic techniques and the available anaesthetic agents, excess secretions from the tracheobronchial tree in adults are not a real problem unless the patient is undergoing instrumentation of the oropharynx or upper airway. Based on these findings, omission of routine anticholinergic premedication has been suggested.⁴⁷ However, as revealed by a survey in 1978,⁴⁰ two thirds of British and Irish anaesthetists still use anticholinergic premedication routinely and the use of glycopyrrolate would appear to be advantageous. One small, but unimportant disadvantage, may be the lack of anti-emetic effect of glycopyrrolate.⁴⁸ It is generally agreed that control of nausea and vomiting is better obtained by specific anti-emetic drugs rather than by anticholinergic premedication.

Children may need routine anticholinergic premedication, both from the point of avoiding excessive secretions in small airways as well as for protection against cholinergic challenges to the heart.⁴⁹ Almost 30 years ago Leigh *et al.*⁵⁰ showed that children were susceptible to bradycardia even with the first dose of suxamethonium and this has been recently confirmed.⁵¹

Glycopyrrolate has been studied in paediatric patients for premedication and been compared with atropine^{19, 52} but mostly by the intravenous route at the time of induction of anaesthesia. One of these studies⁵² although showing little difference between the two drugs regarding the effects on heart rate, found the intra-operative antisialagogue effect of glycopyrrolate to be superior. The other study¹⁹ showed that atropine produced much greater increases in heart rate in comparison to glycopyrrolate, as reported earlier by Myers and Tomeldan.⁵³ In both of these studies, the effect of the two drugs was observed only at 1 and 2 minutes which may give erroneous results since it has been shown in both conscious and anaesthetised children²⁰ and in anaesthetised adults¹⁷ that the peak effect of glycopyrrolate may take about 3 minutes to appear. The more traditional intramuscular route of administration of glycopyrrolate in children has been evaluated only recently⁵¹ although Salem and his colleagues³¹ used this route to evaluate the effects

of premedicants on the pH of gastric contents. Both intramuscular atropine and glycopyrrolate were satisfactory but the use of glycopyrrolate was associated with better control of secretions as well as the occurrence of less serious dysrhythmias.

The intramuscular administration of either atropine or glycopyrrolate does not give sufficient protection whenever there are severe cholinergic challenges to the heart, such as administration of repeated doses of suxamethonium or traction on the extraocular muscles.⁵⁴⁻⁵⁷ In these situations, these drugs often need to be administered intravenously. Glycopyrrolate is more effective than atropine in preventing bradycardia following the administration of repeated doses of suxamethonium.^{58, 59} There are several reports of its use for the prevention of the oculocardiac reflex in children.^{53, 57, 60} All the studies showed that both atropine and glycopyrrolate when administered intravenously in appropriate doses provided similar protection, with glycopyrrolate producing less tachycardia.

Reflex decreases in heart rate in children have been observed when the larynx is sprayed with local anaesthetic; glycopyrrolate in a dose of 7.5 µg/kg has been shown to be effective in preventing this effect.⁶¹

It appears that a routine intramuscular premedicant dose of glycopyrrolate is 0.2–0.4 mg in an adult; the corresponding dose in a child is approximately 10 µg/kg. For intravenous administration where a greater protection against bradycardia is desired, the intravenous dose in an adult is 0.2 mg or, on a weight related basis, 4–5 µg/kg. The dose needs to be somewhat higher in children, particularly where bradycardia is to be avoided; the range of 5–10 µg/kg being adequate.

Glycopyrrolate at the time of antagonism of neuromuscular block

Initial reports of the use of glycopyrrolate in a mixture with neostigmine for antagonism of competitive neuromuscular block appeared in the early 1970s.^{7, 8, 62} It is in this situation that the use of glycopyrrolate is most advantageous. Although atropine and neostigmine have been used to antagonise residual neuromuscular blockade since the introduction of relaxant techniques into anaesthetic practice, this com-

bination is not ideal. Atropine, a tertiary amine, exerts its effects before that of neostigmine which is a quaternary ammonium compound and acts indirectly. Firstly, the relatively large (1–1.5 mg in adults) doses of atropine used produce a sharp rise in heart rate which peaks about 2 minutes after the administration of a conventional reversal 'mixture'. The heart rate then rapidly falls due to the onset of action of neostigmine. Secondly, atropine is relatively shorter acting than neostigmine, and bradycardia and copious oropharyngeal secretions can occur for up to 2 hours after reversal.

A further implication of the non-synchronous nature of atropine and neostigmine is that it is difficult to establish an optimum dose ratio between the two drugs. Inadequate protection of the muscarinic actions of neostigmine can be resolved by increasing the dose of atropine only at the cost of excessive initial tachycardia.⁶³ The pharmacological properties of glycopyrrolate suggest that it would offer advantages over atropine for use as an adjunct to antagonism of neuromuscular block. Most clinical studies have shown that, in practice, glycopyrrolate is a superior alternative to atropine when used at the time of reversal by neostigmine.^{8, 41, 62–67} Given at the time of reversal, glycopyrrolate in a mixture with neostigmine is associated with a much lower initial increase in heart rate and a better protection against anticholinesterase-induced falls in heart rate (Fig. 4). In addition, there is

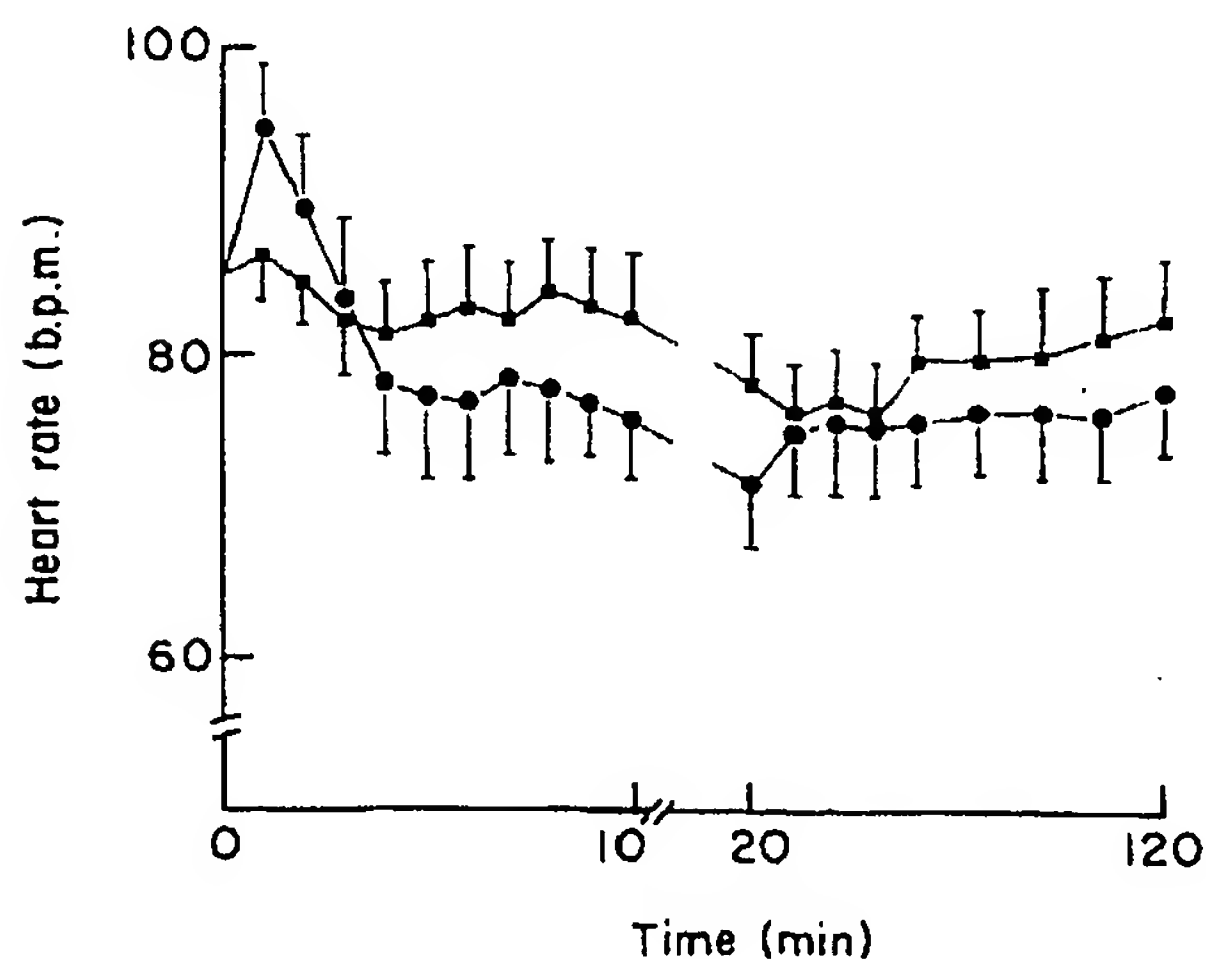


Fig. 4. Heart rate changes following reversal with neostigmine 50 µg/kg with either atropine (●—●) 20 µg/kg or glycopyrrolate (■—■) 10 µg/kg. (Reproduced by kind permission of the Indian Journal of Anaesthesia⁶⁷).

better control of oropharyngeal secretions at extubation than with atropine.

The occurrence of less initial tachycardia with glycopyrrolate in the reversal mixture as compared to atropine is due to the fact that both glycopyrrolate and neostigmine have a similar time to onset of their peak effect, presumably due to their quaternary ammonium structure, and not to any inherent property of glycopyrrolate in producing smaller increases in heart rate at equipotent doses. It has been shown that when used in equipotent doses (half as much of glycopyrrolate as atropine) both drugs produce similar increases in heart rate in anaesthetised patients.^{17, 63, 67} Thus, glycopyrrolate must be slower than atropine in reaching its peak effect as has been clearly demonstrated.¹⁷

The largest study of the use of glycopyrrolate in reversal is that of Cozanitis and his associates.⁶⁶ In this study, 641 patients were assessed under double blind conditions in a 'true to life' situation in which the investigating anaesthetist was free to choose the anaesthetic technique he considered most suited to the patient. At the end of the operation, residual neuromuscular block was reversed with a mixture of neostigmine 50 µg/kg with either atropine 20 µg/kg or glycopyrrolate 10 µg/kg and the patients studied for up to 2 hours after reversal. The results from this study confirmed those reported previously from smaller, better controlled studies.

The heart rate fluctuates markedly after reversal with atropine and neostigmine. These changes can be withstood without untoward sequelae in most healthy young patients. In elderly patients or the patient with pre-existing cardiovascular disease, such changes in heart rate and rhythm during reversal should, ideally, be minimised. The incidence of dysrhythmias has also been reported to be lower in the elderly patients when glycopyrrolate is used instead of atropine with either neostigmine or pyridostigmine.^{68, 69}

In the study by Cozanitis *et al.*,⁶⁶ patients with pre-existing cardiovascular disease were examined as a separate sub-group. The mean heart rates in this group of patients are illustrated in Fig. 5. Those patients reversed with a mixture of neostigmine and glycopyrrolate maintained more stable heart rates during the reversal process; in addition, the number of patients with a heart rate of less than 60 beats per minute in the immediate

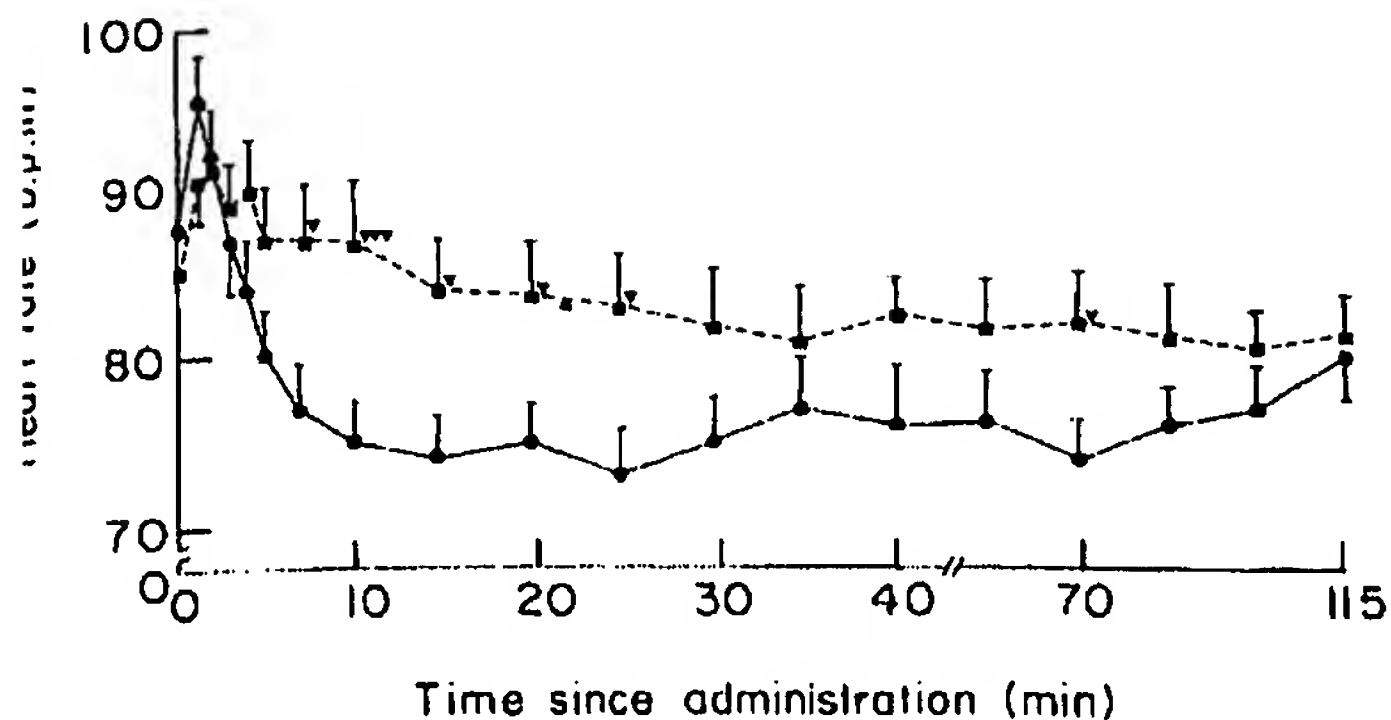


Fig. 5. Mean heart rates after administration of reversal mixtures containing neostigmine 50 $\mu\text{g}/\text{kg}$ with either atropine (\bullet — \bullet) 20 $\mu\text{g}/\text{kg}$ or glycopyrrolate (\blacksquare — \blacksquare) 10 $\mu\text{g}/\text{kg}$ in patients with pre-existing cardiovascular disease, ∇ $p < 0.005$; $\nabla\nabla\nabla$ $p < 0.005$. (Reproduced by kind permission of the British Journal of Anaesthesia.⁶⁶).

post reversal period was significantly less after glycopyrrolate. Both of these factors are of great clinical relevance in such poor risk patients. The superiority of glycopyrrolate in the reversal mixture in patients with cardiac disease was confirmed in a group of patients having undergone closed mitral valvotomies when once again it was shown that glycopyrrolate produced significantly lesser increases in heart rate than atropine.⁷⁰

Studies designed to find the optimum dose and method of administration of atropine or glycopyrrolate with neostigmine showed that the anticholinergic and the anticholinesterase drugs are better administered together rather than separately.^{63, 67} The optimum dosage of glycopyrrolate appears to be about 10 $\mu\text{g}/\text{kg}$ in most cases, although increasing the dose to 15 $\mu\text{g}/\text{kg}$ is not associated with unduly pronounced tachycardia. By contrast, when 20 $\mu\text{g}/\text{kg}$ of atropine was used, about a third of patients required a further dose due to the development of post reversal bradycardia. When the dose of atropine is increased to 30 $\mu\text{g}/\text{kg}$, bradycardia is prevented only at the expense of a more pronounced initial tachycardia.

The advantages of glycopyrrolate over atropine in terms of effects on heart rate are evident even when pyridostigmine is used to reverse the neuromuscular block^{71, 72} and it is likely that a dose smaller than 10 $\mu\text{g}/\text{kg}$ of glycopyrrolate may be sufficient with this anticholinesterase drug. There is no increased incidence of dysrhythmias at reversal in adult

patients when glycopyrrolate is included in the reversal mixture, in fact some studies^{62, 65} have reported a significantly lower incidence. Wong and his colleagues¹⁸ observed that the use of glycopyrrolate was associated with a higher incidence of dysrhythmias when used for reversal of neuromuscular block in paediatric patients having undergone open heart surgery. This has not been observed in any of the numerous subsequent reports on the use of glycopyrrolate in reversal mixtures and a study in otherwise healthy children⁷³ showed that glycopyrrolate possessed the same advantages when used with neostigmine in this group of patients as in adults.

A much superior control of secretions has been a consistent feature of glycopyrrolate as compared with atropine, when used in reversal, as with its uses in premedication. This is, however, not associated with any uncomfortable dryness in the postoperative period.⁷⁴

A further advantage of the use of glycopyrrolate is its absence of central effects, and this has been demonstrated clinically following reversal.^{75, 76} These studies not only confirmed the greater cardiovascular stability with the use of glycopyrrolate in the reversal mixture but also showed that patients were more alert and recovered consciousness more rapidly than when atropine was used. These findings are perhaps due to the poor penetration of glycopyrrolate across the blood brain barrier and is an interesting observation that the central effects of anticholinergic drugs can play a role in modifying the recovery pattern following anaesthesia.

Conclusion

There is little doubt that glycopyrrolate is an effective and potent anticholinergic and is a welcome addition to the drugs that anaesthetists use very frequently. For those who use anticholinergic premedication routinely, it offers several advantages but these are most evident when the drug is used with anticholinesterases as the anticholinergic component of the reversal mixture.

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Mrs V.L. Pooley typed the manuscript.

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